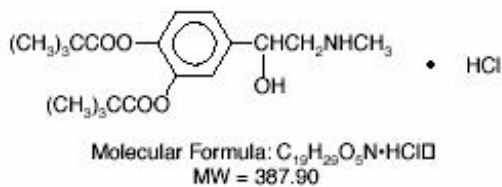


## DIPIVEFRIN HYDROCHLORIDE- dipivefrin hydrochloride solution FALCON Pharmaceuticals, Ltd

### Dipivefrin Hydrochloride Ophthalmic Solution USP, 1%

#### DESCRIPTION

Dipivefrin Hydrochloride Ophthalmic Solution USP, 0.1% is a sterile, isotonic solution. Dipivefrin hydrochloride is a white, crystalline powder, freely soluble in water. It is classified as a sympathomimetic agent and has the following structural formula:



**Chemical Name:** (±) -3, 4-Dihydroxy-a- [(methylamino) methyl] benzyl alcohol 3, 4-dipivalate hydrochloride.

**Contains: Active:** Dipivefrin hydrochloride, 0.1% (1 mg/mL). **Preservative:** Benzalkonium chloride 0.005%. **Inactive Ingredients:** Edetate Disodium, Sodium Chloride, Hydrochloric Acid and/or Sodium Hydroxide (to adjust pH to 2.5 to 3.5), Purified Water. DM-00

#### CLINICAL PHARMACOLOGY

Dipivefrin hydrochloride is a member of a class of drugs known as prodrugs. Prodrugs are usually not active in themselves and require biotransformation to the parent compound before therapeutic activity is seen. These modifications are undertaken to enhance absorption, decrease side effects and enhance stability and comfort, thus making the parent compound a more useful drug. Enhanced absorption makes the prodrug a more efficient delivery system for the parent drug because less drug will be needed to produce the desired therapeutic response.

Dipivefrin is a prodrug of epinephrine formed by the diesterification of epinephrine and pivalic acid. The addition of pivaloyl groups to the epinephrine molecule enhances its lipophilic character and, as a consequence, its penetration into the anterior chamber.

Dipivefrin is converted to epinephrine inside the human eye by enzyme hydrolysis. The liberated epinephrine, an adrenergic agonist, appears to exert its action by decreasing aqueous production and by enhancing outflow facility. The dipivefrin hydrochloride prodrug delivery system is a more efficient way of delivering the therapeutic effects of epinephrine, with fewer side effects than are associated with conventional epinephrine therapy.

The onset of action with one drop of dipivefrin hydrochloride ophthalmic solution occurs about 30 minutes after treatment, with maximum effect seen at about one hour.

Using a prodrug means that less drug is needed for therapeutic effect since absorption is enhanced with the prodrug. Dipivefrin hydrochloride, 0.1% was judged less irritating than a 1% solution of epinephrine hydrochloride or bitartrate. In addition, only 8 of 455 patients (1.8%) treated with dipivefrin reported discomfort due to photophobia, glare or light sensitivity.

## INDICATIONS AND USAGE

Dipivefrin hydrochloride ophthalmic solution is indicated as initial therapy for the control of intraocular pressure in chronic open-angle glaucoma. Patients responding inadequately to other antiglaucoma therapy may respond to addition of dipivefrin.

In controlled and open-label studies of glaucoma, dipivefrin demonstrated a statistically significant intraocular pressure lowering effect. Patients using dipivefrin twice daily in studies with mean durations of 76-146 days experienced mean pressure reductions ranging from 20-24%.

Therapeutic response to 0.1% dipivefrin twice daily is somewhat less than 2% epinephrine twice daily. Controlled studies showed statistically significant differences in lowering of intraocular pressure between 0.1% dipivefrin and 2% epinephrine. In controlled studies in patients with a history of epinephrine intolerance, only 3% of patients treated with dipivefrin exhibited intolerance, while 55% of those treated with epinephrine again developed intolerance.

Therapeutic response to 0.1% dipivefrin twice daily is comparable to 2% pilocarpine 4 times daily. In controlled clinical studies comparing 0.1% dipivefrin and 2% pilocarpine, there were no statistically significant differences in the maintenance of IOP levels for the two medications.

Dipivefrin does not produce miosis or accommodative spasm which cholinergic agents are known to produce. The blurred vision and night blindness often associated with miotic agents are not present with dipivefrin therapy. Patients with cataracts avoid the inability to see around lenticular opacities caused by constricted pupil.

## CONTRAINDICATIONS

Dipivefrin hydrochloride should not be used in patients with narrow angles since any dilation of the pupil may predispose the patient to an attack of angle-closure glaucoma. This product is contraindicated in patients who are hypersensitive to any of its components.

## WARNINGS

NOT FOR INJECTION – FOR OPHTHALMIC USE ONLY.

## PRECAUTIONS

### General

**Aphakic Patients:** Macular edema has been shown to occur in up to 30% of aphakic patients treated with epinephrine. Discontinuation of epinephrine generally results in reversal of the maculopathy.

### Information for patients

To avoid contamination, do not touch tip of container to the eye, eyelid, or any surface.

### Pregnancy

**Pregnancy Category B.** Reproduction studies have been performed in rats and rabbits at daily oral doses up to 10 mg/kg body weight (5 mg/kg in teratogenicity studies), and have revealed no evidence of impaired fertility or harm to the fetus due to dipivefrin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

### Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when dipivefrin hydrochloride is administered to a nursing woman.

## **Pediatric Use**

Safety and effectiveness in pediatric patients have not been established.

## **Animal Studies**

Rabbit studies indicated a dose-related incidence of meibomian gland retention cysts following topical administration of both dipivefrin and epinephrine.

## **ADVERSE REACTIONS**

**Cardiovascular Effects:** Tachycardia, arrhythmias and hypertension have been reported with ocular administration of epinephrine.

**Local Effects:** The most frequent side effects reported with dipivefrin hydrochloride alone were injection in 6.5% of patients and burning and stinging in 6%. Follicular conjunctivitis, mydriasis and allergic reactions to dipivefrin have been reported infrequently. Epinephrine therapy can lead to adrenochrome deposits in the conjunctiva and cornea.

## **DOSAGE AND ADMINISTRATION**

**Initial Glaucoma Therapy.** The usual dosage of dipivefrin hydrochloride ophthalmic solution, 0.1%, is one drop in the eye(s) every 12 hours.

**Replacement With Dipivefrin Hydrochloride Ophthalmic Solution:** When patients are being transferred to dipivefrin from antiglaucoma agents other than epinephrine, on the first day continue the previous medication and add one drop of dipivefrin to each eye(s) every 12 hours. On the following day, discontinue the previously used antiglaucoma agent and continue with dipivefrin.

In transferring patients from conventional epinephrine therapy to dipivefrin, simply discontinue the epinephrine medication and institute the dipivefrin regimen.

**Addition of Dipivefrin Hydrochloride Ophthalmic Solution:** When patients on other antiglaucoma agents require additional therapy, add one drop of dipivefrin every 12 hours.

**Concomitant Therapy.** For difficult to control patients, the addition of dipivefrin hydrochloride ophthalmic solution to other agents such as pilocarpine, carbachol, echothiophate iodide or acetazolamide has been shown to be effective.

**Note:** Not for injection.

## **HOW SUPPLIED**

Dipivefrin Hydrochloride Ophthalmic Solution USP, 0.1% is supplied sterile in opaque plastic DROP-TAINER® Dispensers as follows:

5 mL–NDC 61314-235-05

10 mL–NDC 61314-235-10

15 mL–NDC-61314-235-15

## **Special handling and Storage Conditions**

Store at controlled room temperature 15°-30°C (59°-86°F) in a tight, light-resistant container.

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**Rx Only**



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## DIPIVEFRIN HYDROCHLORIDE

dipivefrin hydrochloride solution

### Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:61314-235
<b>Route of Administration</b>	OPHTHALMIC	<b>DEA Schedule</b>	

### Active Ingredient/Active Moiety

<b>Ingredient Name</b>	<b>Basis of Strength</b>	<b>Strength</b>
dipivefrin hydrochloride (UNII: 5QTH9UHV0K) (dipivefrin - UNII:8Q1PVL543G)		1 mg in 1 mL

### Inactive Ingredients

<b>Ingredient Name</b>	<b>Strength</b>
benzalkonium chloride ( )	0.05 mg in 1 mL
edetate disodium (UNII: 7FLD91C86K)	
sodium chloride (UNII: 451W47IQ8X)	
hydrochloric acid and/or sodium hydroxide ( )	
water (UNII: 059QF0KO0R)	

### Packaging

#	<b>Item Code</b>	<b>Package Description</b>	<b>Marketing Start Date</b>	<b>Marketing End Date</b>
1	NDC:61314-235-05	5 mL in 1 BOTTLE, PLASTIC		
2	NDC:61314-235-10	10 mL in 1 BOTTLE, PLASTIC		
3	NDC:61314-235-15	15 mL in 1 BOTTLE, PLASTIC		

**Labeler** - FALCON Pharmaceuticals, Ltd